Comments on the FDA's Draft Guidance for Industry: Antiviral Drug Development-Conducting Virology Studies and Submitting the Data to the Agency
Draft Guidance

We commend and thank the agency for assembling and providing the above referenced draft guidance document and for soliciting comments and suggestions for consideration before finalizing the Guidance. The agency has put together a thoughtful and comprehensive draft guidance document on the subject of virology studies and associated data submission in support of the development of antiviral drugs. The document is a valuable communication for all stakeholders to understand the Agency's current thinking about the content and timing of such studies and provides an important guide to the Agency's expectations. This information is particularly important to Industry stakeholders allowing them to plan, configure, and resource drug discovery and development programs appropriately to meet these expectations in a timely manner.

Overall Comments

While overall we believe the current draft guidance document represents a thorough assembly of pre-clinical and clinical virology studies to understand the activity, factors that can influence this activity, mechanism of action, genetic basis for resistance and potential for drug-drug interactions that may be beneficial or of potential concern, there are several aspects to the draft guidance that we feel deserve additional consideration or clarification. These aspects can be broadly grouped into three categories, one relating to development of drugs acting at novel targets and/or through novel mechanisms, one concerning the timing of certain studies with particular reference to those required prior to first time in man proof of concept studies, and one relating to requirements for assessing potential interactions with other investigational (as opposed to approved) antiviral agents.

Specific Comments:

Lines 77-78 "Determining the antiviral activity of an investigational drug against viruses resistant to **other drugs** with the same molecular target"

We recommend that the agency clarify the meaning of "other drugs". Is the agency recommending that these studies evaluate the antiviral activity against viruses resistant to approved drugs or to approved and investigational drugs with the same molecular target? Practical considerations (difficulty or inability to obtain other investigational compounds for a variety of reasons as well as information concerning genetic determinants of resistance to other investigational agents) lead us to recommend that the agency consider recommending these studies with only approved agents with the same molecular target.

Lines 87-90 "We suggest that sponsors complete in vitro drug combination activity studies of the investigational drug with the approved drugs before the initiation of clinical trials that will examine the efficacy of the investigational drug in combination with approved drugs."

We request that the agency consider specifying whether these in vitro combination studies need to be carried out with all approved drugs or with representative approved drugs from all existing classes, or with only those drugs that will be used in the clinical trial prior to the initiation of clinical trials that will examine the efficacy of the investigational drug in combination with approved drugs. This can be a difficult requirement for investigational agents acting at novel targets as the experimental systems for evaluating their activity may not be susceptible to agents acting at some other targets. Research use type assays may be the only means of assessing such potential interactions in vitro and there should be some recognition or acknowledgement of this.

Lines 90-93 "Furthermore, we recommend examining the in vitro selection of resistant viruses to the investigational drug, the phenotypic and genotypic characterization of the resistant viruses, and cross-resistance analyses before initiation of clinical studies in patients infected with the particular virus."

For drugs acting at established targets, this recommendation is acheiveable and reasonable. However, for drugs acting at novel targets or through novel mechanisms the determinants of resistance may be incompletely or poorly understood. Given the high medical need for compounds acting at novel targets, we recommend that requirements prior to proceeding into clinical studies be less restrictive. Often, it is only possible to gain sufficient insight into the determinants and mechanisms of resistance through clinical trials and these insights are often critical guides to the studies described above in lines 90-93.

Lines 101-104 "We prefer that mechanism of action studies be conducted before the initiation of phase 1 clinical studies. Nonclinical virology reports on the mechanism of action should include background information and data identifying the mechanism of action of the investigational drug and its metabolites."

In vitro and animal systems are often not adequate to fully identify metabolites of investigational drugs of importance that will be generated in vivo in humans. The draft guidance on this issue would require synthesis, characterization and in depth MOA studies on metabolites identified through these surrogate systems prior to the initiation of phase I proof of concept studies. Given the uncertain value of these studies on metabolites identified in surrogate systems as predictors of in vivo efficacy or toxicity, and the extensive nature of the resources required for such studies, we recommend that such studies on metabolites be conducted after proof of concept studies in humans with metabolites identified in those studies.

Lines 147-149 "we recommend that the sponsor document that the investigational drug and/or its metabolites show specific, quantifiable antiviral activity in vitro before initiating tests in humans (i.e., before initiation of phase 1 studies).

Same considerations and recommendations as above for lines 101-104 of the draft guidance.

Lines 164-166 "Evaluating the antiviral activity of the investigational drug against mutant viruses that are resistant to drugs with the same molecular target as the investigational drug as well as viruses resistant to other drugs for the same indication

Same considerations and recommendations as above for Lines 77-78 of the draft guidance.

Lines 179-181 "An investigational drug that inhibits virus replication at concentrations lower than biochemical data for the proposed mechanism indicates that another target or mechanism of inhibition may be affected.

While we agree that if a drug displays antiviral activity at concentrations lower than biochemical data for the proposed mechanism it may suggest that another target or mechanism of action may be at work, such results may also reflect different sensitivities in the biochemical and biological assays used to assess antiviral activity and mechanism of action. We would recommend in any updated version of this guidance document that this sentence either be removed or amended to acknowledge the potential for differing assay sensitivities to contribute to such results.

Lines 214-219 "If the investigational drug is highly protein bound, sponsors are encouraged to examine the in vitro antiviral activity of the investigational drug in the presence of increasing concentrations of human serum up to 40 to 50 percent. An IC_{50} for 100-percent human serum can be extrapolated from this data and the serum adjusted IC_{50} values reported. Sponsors are also encouraged to determine IC_{50} values in the presence of 2 mg/mL α-acidic glycoprotein."

We agree with the agency's recommendation encouraging sponsors to examine the influence of serum proteins on the in vitro antiviral activity of investigational drugs that are highly protein bound. However, we do not believe there is a clearly established and validated method for extrapolating IC50 values derived in the presence of 50% normal human serum to the actual antiviral activity attained in the presence of 100% serum and recommend removing from the recommendations the extrapolation to 100% serum.

Lines 223-232 "Information on plasma and intracellular drug concentrations is important in assessing the dose/response of antiviral therapy and evaluating the potential for resistance development; therefore, it is useful to determine an inhibitory quotient (IQ).[2] (For more information on determining IC_{50} values, see Section III.B.2.a., Antiviral activity in vitro.) We view IQ ratios as a useful tool integrating in vivo drug concentrations and antiviral activity. It is a measure that characterizes the relationship between drug exposure and the susceptibility of a virus to a drug. A high IQ indicates an effective drug concentration can be achieved in a patient to inhibit the virus and minimize the development of drug resistance. Since one dose may not be adequate for all patient populations, IQ ratios can be used to aid in the selection of a dose or doses to further evaluate in phase 3 clinical studies."

The predictive value of IQ for classes of anti-HIV drugs other than protease inhibitors has not be established. In particular the relationship of IQ values to in vivo activity of entry inhibitors has yet to be shown. Therefore, we recommend that the agency characterize these studies as investigational for various classes of investigational drugs until and unless their utility can be established with the particular class in question.

Lines 258-266 "We recommend determining CC_{50} values in both stationary and dividing cells from multiple human cell types and tissues for potential cell-cycle, species, or tissue-specific toxicities. We prefer that studies determining cytotoxicity/therapeutic index be conducted before the initiation of phase 1 clinical studies.
Because of the myelosuppressive effects of certain antiviral drugs, we recommend assessing the potential effects of certain candidate drugs on the growth of human bone marrow progenitor cells in colony formation assays."

Conducting a thorough evaluation of the safety of an investigational drug is a critical component of the drug development process and needs to occur early on. The use of parallel cytotoxicity assays and antiviral assays is essential to distinguish specific antiviral effects from cytotoxic effects on host cells and may be most informative when performed in the same cell type. However, the extensive series of in vitro evaluations recommended above may not provide further insight into the potential for toxicities of an investigational drug than that obtained through the traditional nonclinical toxicology studies currently performed prior to initiation of first time in man studies. We recommend that the nonclinical toxicology studies are a more appropriate and informative venue for assessing these potential risks.

Lines 282-289 "we recommend that sponsors evaluate the in vitro antiviral activity of investigational drugs in two- or three-drug combinations with other drugs approved for the same indication. We also recommend completing the in vitro drug combination activity studies of approved drugs with the investigational drug prior to initiation of the clinical trials that will evaluate the efficacy of the combination of the investigational drug with approved drugs. Often subjects are infected with two or more viral diseases (e.g., HIV and HBV or HCV); therefore, we recommend that the in vitro antiviral activity of antiviral drugs used in co-infected patients for different indications be assessed in in vitro combination activity studies."

Combination studies involving two drugs to determine synergistic, additive or antagonistic activities are used routinely. Analysis of 3-drug combinations is considerably more challenging and lacking in standardized methods of evaluation. We assert that two drug combination studies are likely to provide the desired information and therefore recommend removal of the request for 3-drug combination studies from the agency's guidance.

The section recommending combination studies for antiviral drugs used in co-infected patients for different indications should be restricted to those cases where a scientific rationale for a potential interaction exists.

Lines 296-301 "We recommend that the in vitro selection of resistant viruses to the investigational drug, the phenotypic and genotypic characterization of resistant viruses, and cross-resistance analyses be examined before initiation of clinical studies in patients infected with the particular virus. The completion of in vitro resistance selection studies is recommended to assess the potential of a target virus to mutate and develop reduced susceptibility (i.e., resistance) to the investigational drug."

We agree with the agency on the importance of identifying resistance to new investigational drugs. In vitro selection is often the first setting for obtaining such resistance data and provides an important opportunity to link genetic changes with phenotypic effects. However, it is often not possible (due to the inability to generate sufficient numbers of resistant variants from sufficiently diverse virus populations) nor practical (due to the length in time – which can, in some cases, take years in vitro for agents with particularly high genetic barriers) to require the "completion" of in vitro resistance selection studies prior to the initiation of clinical studies. In addition, agents acting at highly variable targets such as the HIV-1 envelope gp160 add further to the complexities associated with resistance studies. In addition, for agents acting at novel targets or through novel mechanisms there may not be a standardized assay or approach to these assessments and in fact such approaches and assays may be in development as well. In view of the medical need for investigational drugs acting at new targets or through novel mechanisms for HIV-1 infection, we recommend removing the requirement for "completion" of these studies before initiation of clinical studies. Further, we recommend that in the case of investigational drugs acting at novel targets or through novel mechanisms that the requirements for selecting and characterizing resistant viruses prior to Phase I as well as the requirements for the assays and approaches used to conduct the genotypic and phenotypic evaluations of viruses resistant to these investigational drugs be flexible. We suggest the agency reframe the recommendations to ensure that the studies required provide a sufficient guide for clinical study design and appropriate analytical approaches as well as exploration of the potential barrier to resistance. The results from the in vitro preclinical studies in combination with the results from the clinical trials (often extending beyond those conducted during Phase II) will be required to fully characterize the genetic determinants and mechanisms of resistance and their linkage to phenotypic effects.

Lines 320-323 "Sponsors are encouraged to assess the development of resistance in vitro over the concentration range spanning the anticipated in vivo concentration and to determine if the same or different patterns of resistance mutations develop by repeating the selection of variants resistant to the investigational drug several times."

For in vitro resistance selections with investigational drugs that take particularly long periods of time to yield resistant viruses (as with some agents with particularly high genetic barriers) and for those targeting highly variable genes (for example the HIV-1 envelope gp160) it may be equally or more informative to perform selections with several different viruses as opposed to repeating the selection process several times with the same virus. Changes observed with in vitro selections can be examined fruitfully through alternative means such as site directed mutagenesis. We recommend that the agency

consider encouraging sponsors to assess the development of resistance in vitro over concentration ranges spanning the anticipated in vivo concentration by conducting the selection of viruses resistant to the investigational drugs with several different virus populations that include (but are not necessarily limited to) primary viruses.

Lines 333-334 "In the second method, virus is passaged in the presence of increasing drug concentrations starting at half the IC_{50} value for the parental virus."

The most efficient and effective way to select for resistant viruses in vitro can vary according to the agent employed. Therefore, we recommend amending the guidance to reflect starting at a concentration relative to the IC50 appropriate for the investigational drug under study.

Lines 349-351 "It is preferable to characterize resistance pathways in several genetic backgrounds (i.e., strains, subtypes, genotypes) and to obtain isolates during the selection process to identify the order in which multiple mutations appear."

We ask the agency to clarify the timing of the requested resistance information with respect to studies in various viral subtypes. While we agree that such information is important to understand the similarities and differences in resistance pathways that might be evident in differing subtypes and ultimately to provide useful information in the setting of clinical practice, we suggest that the agency consider recommending such studies in multiple viral subtypes commencing after the initial proof of concept Phase I studies.

Lines 369-374 "The shift in susceptibility (or fold resistant change) for a viral isolate should be measured by determining the IC_{50} values for the isolate and comparing it to the IC_{50} value of a reference virus done under the same conditions and at the same time. The fold resistant change should be calculated as the IC_{50} value of the isolate/IC_{50} value of the reference strain. We recommend that a well-characterized wild-type laboratory strain grown in cell culture serve as a reference standard."

While we agree with the guidance that comparisons of shifts in susceptibility relative to a reference strain can provide a useful measure, for agents that have broad susceptibility ranges for wildtype viruses we consider the fold shift from the parental or starting virus to be a more direct measure of impact of resistance. We suggest that the agency's guidance allow for the inclusion of such measures for investigational drugs where these comparisons may provide more meaningful insights.

Lines 605-613 Appendix 1: Template for Submitting HIV Resistance Data

"Approved/investigational anti-HIV agents (List first agents in the same class in alphabetical order followed by agents with the same target protein in alphabetical order. End with agents outside drug class in alphabetical order.)

- Fold change in IC_{50} value of baseline compared to reference strain for all approved/investigational anti-HIV agents

- Fold change in IC_{50} value at time of endpoint assessment or failure compared to reference strain for each of the approved/investigational anti-HIV agents
- Fold change in the IC_{50} value at time of endpoint assessment or failure compared to baseline for each of the approved/investigational anti-HIV agents"

As mentioned previously in our comments above, there can be many issues that would prevent a sponsor from being able to obtain other investigational agents for these studies. We recommend that the agency eliminates other investigational agents as a requirement in this guidance document.